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The Radiological Differentiation of Hypervascular Intrahepatic Cholangiocarcinoma from Hepatocellular Carcinoma with a Focus on the CT Value on Multi-phase Enhanced CT

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Abstract. *Background/Aim: This study aimed to investigate whether hypervascular intrahepatic cholangiocarcinoma (HICC) can be differentiated from hepatocellular carcinoma (HCC). Materials and Methods: Among 100 patients with intrahepatic cholangiocarcinoma, 22 patients were diagnosed with HICC based on the computed tomography (CT) value in the late arterial phase as follows: the CT value of the tumor ≥ that of the liver parenchyma. The CT values of the HICC were compared to those of HCC cases (n=120). Results: The CT value of HICC was lower in the unenhanced phase (UP) (p=0.016) and higher in the equilibrium phase (EP) (p<0.001) in comparison to HCC. The non-tumorous liver (odds ratio [OR]: 6.35, p=0.002) and an E/U ratio (the mean CT value of the tumor in the EP to that in the UP) of >2.3 (OR=13.1, p<0.001) were independent diagnostic factors for differentiating HICC from HCC. Conclusion: E/U ratio is useful for differentiating between HICC and HCC.*

Intrahepatic cholangiocarcinoma (ICC) is the second most common hepatic malignancy worldwide, following hepatocellular carcinoma (HCC) (1, 2). Computed tomography (CT) is the first-line imaging method used to evaluate liver tumors. The typical radiographic features of ICC include a hypovascular tumor with rim enhancement throughout both the arterial and portal venous phases, intrahepatic biliary dilatation, and delayed enhancement from the peripheral to the central part of the tumor (3-6). However, some cases of ICC show a hypervascular appearance in the arterial phase of enhanced CT (7-11). In patients with hypervascular ICC (HICC), the tumor is sometimes radiographically misdiagnosed as other liver tumors, especially HCC, that show early enhancement (5, 10, 12). It was recently reported that ICCs often show early enhancement, especially in patients with chronic viral hepatitis or cirrhosis (4, 8), which complicates the differential diagnosis of HICC and HCC, because the background liver is an important risk factor for HCC. In addition, ICCs often develop lymph node metastases (13), whereas HCCs rarely develop lymph node metastases (14-16). The surgical strategy, including the necessity of lymph node dissection and the extent of the surgical margin differ between ICC and HCC. Thus, a correct preoperative differential diagnosis is important for overcoming these cancers. This study compared the CT values of HICC and HCC in each phase of multi-phase enhanced CT and investigated whether HICC can be accurately differentiated from HCC based on the tumor's CT value.

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Key Words: Intrahepatic cholangiocarcinoma, hepatocellular carcinoma, multidetector computed tomography, differential diagnosis.

Patients and Methods

Patient selection. From January 2003 to June 2015, 726 patients with primary liver cancers underwent macroscopic curative hepatectomy at the division of the Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, Japan. A total of 100 patients had ICC, 588 patients had HCC, 28 patients had combined hepatocellular-cholangiocarcinoma, 4 patients had double cancer of ICC and HCC, and 6 patients had others (Figure 1). ICCs were macroscopically classified into three types according to their morphology and growth pattern: mass forming (MF)-type, periductal infiltrating (PI)-type, intraductal growth (IG)-type (17). Of these, we retrospectively studied 77 patients with MF-type and predominantly MF-type ICC (MF + PI-type and MF + IG-type). If a tumor had a higher mean CT value than that of liver parenchyma

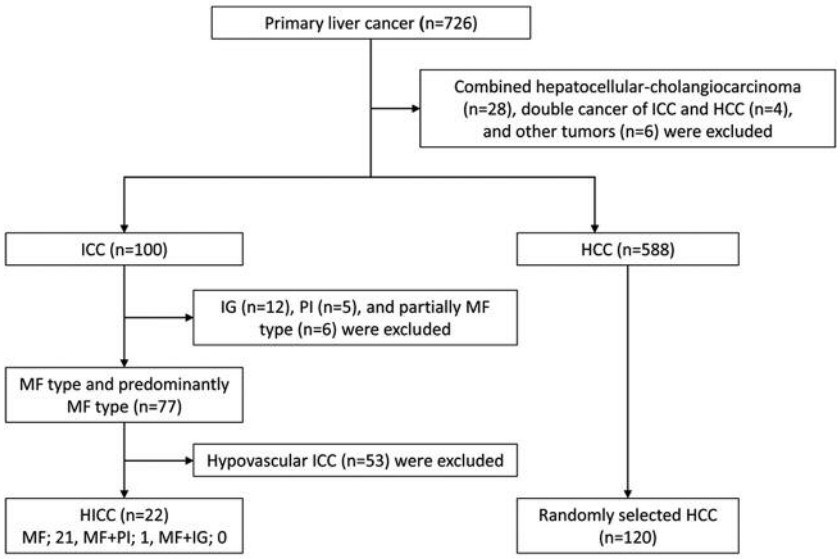

Figure 1. *A flow chart of patient enrolment. (a) HICC group; (b) HCC group.*

in the late arterial phase, the tumor was defined hypervascular ICC (HICC). Among 77 ICC patients, 22 patients (22 tumors, MF-type, n=21; MF- + PI-type, n=1) fit the definition. One hundred twenty of 588 HCC patients (164 tumors, including 4 scirrhous HCCs) were extracted to control the ratio of the HCC number to HICC number as 5:1 within each year. The timing of resection had been considered as confounding to reduce potential errors.

In patients with multiple lesions, only the largest lesion was selected for CT evaluation. The final diagnoses of the tumors were confirmed based on the histopathological examination of surgical specimens. Patients with small tumors that were unmeasurable in >3 slices, those in whom CT was performed at another hospital, and those with CT images obtained from <3 phases were excluded. Patients who underwent pre-therapeutic procedures such as re-hepatectomy, trans-catheter arterial chemoembolization, and chemotherapy were also excluded. We collected and assessed the patients' clinical data from our database and institutional medical records. The Institutional Review Board approved the retrospective collection and the analysis of the data in this study.

CT image acquisition. Between 2003 and 2008, CT scans were performed with a 16-detector CT scanner (Aquilion 16; Toshiba Medical System, Tokyo, Japan); thereafter, they were performed with a 320-detecter CT scanner (Aquilion ONE; Toshiba Medical System, Tokyo, Japan). The image acquisition settings were as follows: tube voltage, 120 kVp; rotation time, 0.5 s; slice thickness, 1.0 mm; reconstruction interval, 1 mm (0.5 mm overlap). The tube current was determined by an automatic exposure control system. Enhanced CT was performed in 3 phases: unenhanced phase (UP), late arterial phase (LAP), portal vein phase (PVP), and equilibrium phase (EP). Images were obtained after the intravenous administration of 150 ml of 350 mgI/ml iopamidol (Iopamiron; Nihon Schering Co, Ltd, Tokyo, Japan) using a calibrated power injector (Auto Enhance A-50; Nemoto Kyorindo, Tokyo, Japan) at a rate of 4 ml/sec. The LAP, PVP, and EP scans were started approximately 35, 75 and 180 sec, respectively, after the start of the contrast material injection. These scanning protocols did not change during the study period.

CT value measurement. All CT images were evaluated on a multi-modality picture archiving and communication system (Synapse workstation software, FUJIFILM, Tokyo, Japan). We traced the tumor shape precisely and measured the mean CT value of the tumor in the axial section in arbitrary three slices, including the largest dimension of the tumor (Figure 2), and the mean CT value of three slices was calculated on each phase. To measure the CT value of the non-tumorous liver parenchyma, a round or ovoid region of interest (ROI) was set, excluding non-liver structures when possible, on the right liver lobe (2 areas), and left lobe (1 area) in each phase, and the mean CT value of these 3 areas was calculated. When the mean CT value of the spleen was higher than that of the liver parenchyma, the patient was diagnosed as having fatty liver. All CT images were evaluated by an independent reviewer (T.A.) who was blinded to the original interpretations and outcomes.

Statistical analysis. Differences in the numerical data of the two groups were examined by the χ^2 test or Fisher's exact test (when n<5). Differences in quantitative variables were evaluated by the Mann-Whitney *U*-test. A multivariate logistic regression analysis was performed to identify factors predicting a diagnosis of HICC; variables with a *p*-value of <0.1 were entered into the final model. Tumor markers were not entered into the model because the data were insufficient. The tentative cut-off CT value of the tumor that maximized the difference in the diagnosis of HICC was determined using the area under the curve (AUC) value, which was calculated from a receiver operating characteristic (ROC) curve analysis. Statistical analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Table I. *The characteristics of patients in the hypervascular intrahepatic cholangiocarcinoma and hepatocellular carcinoma groups.*

	HICC (n=22)	HCC (n=120)	*p*-Value
Gender			
Male/female	13/9	93/27	0.106
Age			
Median (range)	68 (59-75)	70 (41-83)	0.201
BMI (kg/m^2)			
Median (range)	23.1 (13.5-30.2)	23.4 (15.9-38.2)	0.638
HBs-Ag			
Present	3 (14%)	21 (18%)	1
HCV-Ab			
Present	4 (18%)	53 (44%)	0.032
CEA (ng/ml)			
Median (range)	2.4 (1.3-640)	2.9 (0.8-11.9)	0.816
CA19-9 (U/ml)			
Median (range)	33.0 (2.0-197)	18.5 (2.0-164)	0.004
AFP (ng/ml)			
Median (range)	3.7 (1.5-58.6)	24.3 (0.7-245000)	<0.001
PIVKA-II (mAU/ml)			
Median (range)	19.0 (8.0-33.0)	224 (11-187000)	<0.001
Fatty liver			
Present	1 (1%)	10 (1%)	1
Preoperative diagnosis			
Correct	13 (59%)	118 (98%)	<0.001
Tumor size (mm)			
Median (range)	51.0 (20.0-120.0)	40.0 (12.0-180.0)	0.417
Tumor differentiation			0.807
Well	4 (18%)	20 (17%)	
moderate	15 (68%)	93 (78%)	
Poor	1 (5%)	6 (5%)	
Unknown	2 (9%)	1 (1%)	
Portal vein invasion			
Present	3 (14%)	31 (26%)	0.922
Hepatic vein invasion			
Present	3 (14%)	11 (9%)	0.388
Arterial invasion			
Present	0 (0%)	1 (1%)	1
Bile duct invasion			
Present	4 (18%)	4 (3%)	0.003
Lymph node dissection			
Present	12 (55%)	2 (2%)	<0.001
Lymph node metastasis			
Present	0 (0%)	1 (1%)	1
Non-tumorous liver parenchyma			<0.001
Normal	11 (50%)	15 (13%)	
Chronic Hepatitis	7 (32%)	58 (48%)	
Liver fibrosis	4 (18%)	14 (12%)	
Liver cirrhosis	0 (0%)	33 (28%)	

HICC: Hhypervascular intrahepatic cholangiocarcinoma; HCC: hepatocellular carcinoma; BMI: body mass index; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; CEA: carcinoembryonic antigen; CA19-9: cancer-associated carbohydrate antigen 19-9; AFP: alfa-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

Results

Patient characteristics. There were no significant differences in sex, age, or body mass index between the two groups (p=0.201, p=0.106, p=0.638, respectively) (Table I). The carbohydrate antigen 19-9 (CA19-9) level of the HICC group was higher than that of the HCC group (p=0.004); however, the levels of alpha-fetoprotein (AFP) (p<0.001) and protein induced by vitamin K absence or antagonist II (PIVKA-II) (p<0.001) in the HICC group were lower than those in the HCC group. Only 13 of 22 patients (59%) in the HICC group were diagnosed correctly with ICC before hepatectomy; in contrast, 118 patients (98%) with HCC were correctly diagnosed. The incorrect preoperative diagnoses in the HICC group were HCC (n=5), combined hepatocellular and cholangiocarcinoma (n=4), and metastatic liver cancer (n=1). The median tumor size was not significantly different between the groups (51.0 mm *vs*. 40.0 mm, p=0.417).

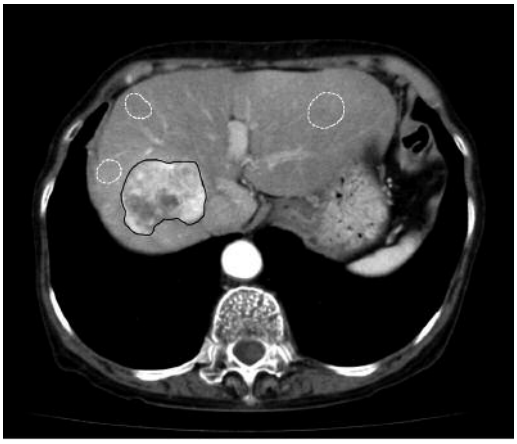

Figure 2. *Measuring the CT values of the tumor and non-tumorous liver parenchyma. We traced the tumor shape precisely and measured the mean CT value of the tumor on an axial section in three arbitrary slices, including the largest dimension of the tumor (black line). The mean CT value of three slices was calculated. When measuring the CT value of the non-tumorous liver parenchyma, a round or ovoid region of interest (ROI) was set on the right liver lobe (2 areas), and left lobe (1 area) in each phase (white dashed line), and the mean CT value of these 3 areas was calculated.*

Pathologically, well-to-moderately differentiated tumors were common in both groups. The incidence of bile duct invasion in the HICC group was higher than that in the HCC group (55% *vs*. 7%, p=0.003). Lymph node dissection was performed in 12 patients (55%) in the HICC group and 2 patients (2%) in the HCC group (p<0.001). As for the pathological findings of the non-tumorous liver parenchyma, half (50%) of the HICC patients had chronic hepatitis or cirrhosis, whereas 88% of the HCC patients had chronic hepatitis or cirrhosis.

CT values. The CT values of the non-tumorous liver parenchyma in the UP (58.6 HU *vs*. 57.0 HU, p=0.132), LAP (75.9 HU *vs*. 79.4 HU, p=0.662), PVP (117.5 HU *vs*. 114.5 HU, p=0.462), and EP (99.1 HU *vs*. 97.5 HU, p=0.515) were comparable between the two groups (Figure 3a). The CT values of the HICC group were significantly

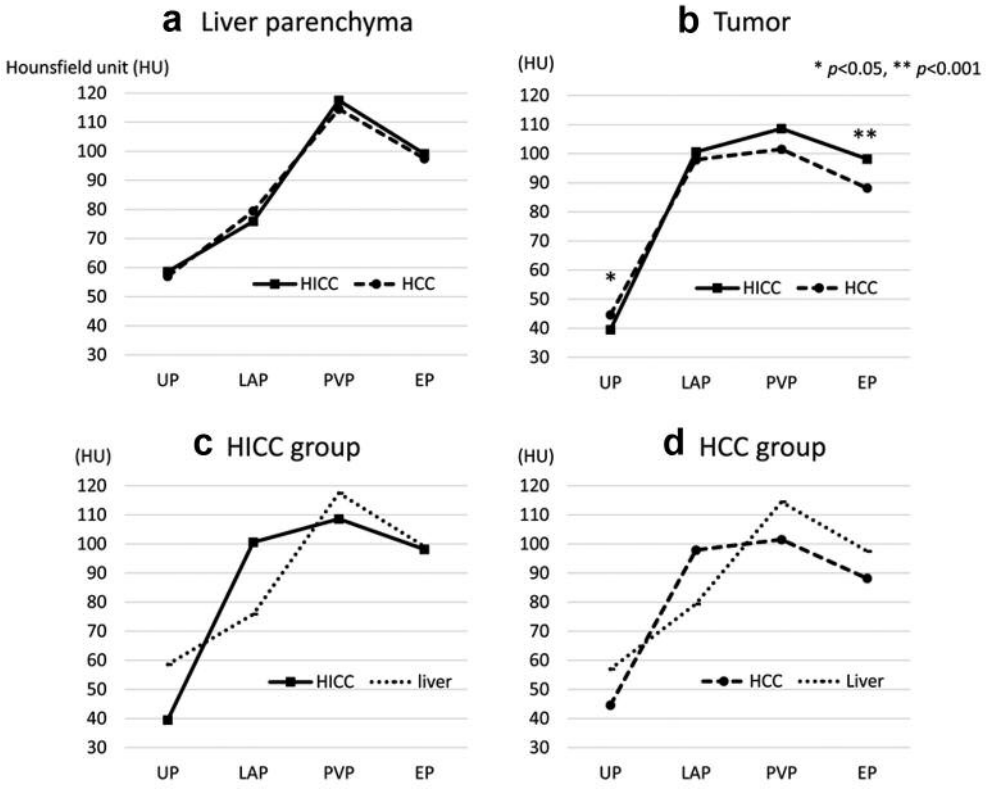

Figure 3. *The CT value in each phase of enhanced CT. A graph illustrating the CT value of the (a) liver parenchyma in the HICC and HCC groups, (b) the tumor in the HICC and HCC groups, (c) the tumor and liver parenchyma in the HICC group, (d) the tumor and liver parenchyma in the HCC group. The CT value of the liver parenchyma in each phase was comparable between the two groups (a). The CT value of the HICC group was lower than that of the HCC in the UP (39.5 HU vs. 44.6 HU, p=0.016), and higher than that of the HCC in the EP (98.2 HU vs. 88.2 HU, p<0.001). There was no difference between two groups in the arterial phase (p=0.438) or portal phase (p=0.124) (b). The CT value of the HICC group in the EP was almost equal to that of the liver parenchyma (c), whereas the CT value of the HCC group in the EP was 10 HU lower than that of the liver parenchyma (d).*

lower in the UP (39.5 HU *vs.* 44.6 HU, p=0.016) and significantly higher in the EP (98.2 HU *vs.* 88.2 HU, p<0.001) in comparison to HCC, while the CT value of the tumor in the LAP (100.6 HU *vs.* 97.9 HU, p=0.438), and PVP (108.6 HU *vs.* 101.5 HU, p=0.124) were comparable between the two groups (Figure 3b). In comparison to the non-tumorous liver parenchyma, the CT value of HICC in the EP was almost equal to the surrounding liver parenchyma while that of HCC was approximately 10 HU lower than the surrounding liver parenchyma (Figure 3c and d).

Based on these differences, we defined the E/U ratio (the ratio of the mean CT value of the tumor in the EP to that of the tumor in the UP). The mean values of the 75th percentile of the E/U ratio of HICC and HCC were 2.45 and 1.97, respectively (p<0.001) (Figure 4a). The ROC analysis for differentiating between HICC and HCC showed that an E/U ratio of 2.3 provided the greatest sensitivity (77%) and specificity (86%); AUC was 0.85 (Figure 4b). The univariate and multivariate analyses revealed that normal non-tumorous liver (odds ratio [OR]: 6.35, p=0.002) and an E/U ratio of >2.3 (OR=13.1, p<0.001) were significant, independent diagnostic factors for differentiating HICC from HCC (Table II). When the liver tumor occurred with both factors, the proportion of HICC patients was 70%, while the proportion was 3% when without factors.

Discussion

Our data suggest that HICC can be differentiated from HCC based on threshold CT values in the UP and EP. The combination of the CT values in the two phases was more useful because it amplified the difference between HICC and HCC. Unlike complicated methods requiring instruments and special skills, measuring the CT value is an easy, quick and non-invasive method that can be applied in daily clinical practice. Although tumor biopsy is useful for evaluating

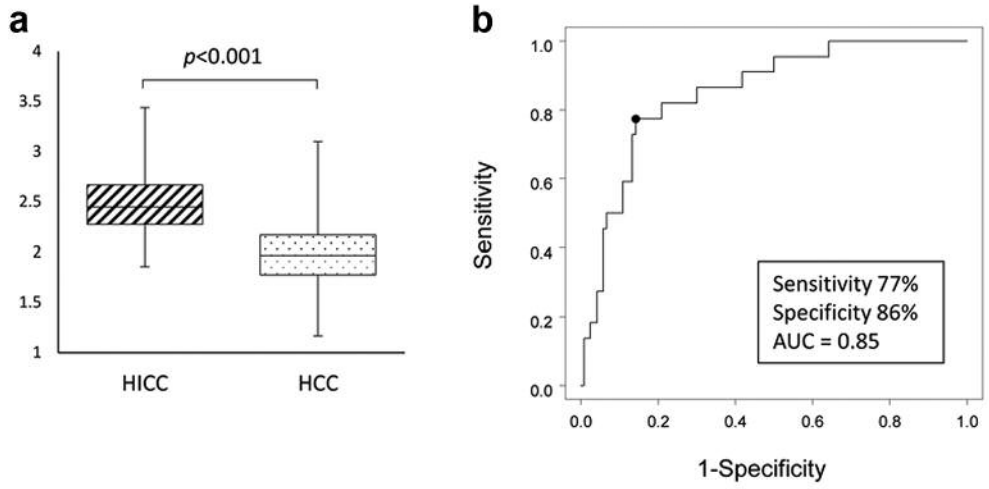

Figure 4. *The E/U ratio. The boxplot shows the distribution of the E/U ratios in differentiating between HICC and HCC. The mean values of the 75th percentile E/U ratio of HICC and HCC were 2.45 and 1.97, respectively (p<0.001) (a). The ROC analysis for differentiation between HICC and HCC showed that a threshold E/U ratio of 2.3 provided the greatest sensitivity (77%) and specificity (86%). The AUC of this threshold was 0.85 (b).*

unknown liver tumors, it is invasive and not always feasible for patients with bleeding disorders. Moreover, tumor biopsy should be reduced in order to minimize the risk of tumor seeding (4). Thus, it is useful to determine the definite diagnosis with a non-invasive method using limited information about the tumor.

Delayed or prolonged enhancement area inside the liver tumor on CT is widely considered to histopathologically correspond to fibrotic stroma (18, 19). The cause is reported to be the slow wash-in and wash-out of the extravascular flux of iodinated contrast material in fibrous tissue (20). ICC is well known as a representative liver tumor with rich fibrous tissue (1, 18, 19). In contrast, with the exception of special types, including scirrhous HCC, fibrolamellar carcinoma, and post-therapeutic carcinoma, intratumoral fibrosis is rarely seen in HCC. In the present study, this finding was only observed in 4 patients (all scirrhous HCC). Although HICC has sometimes been reported to be less fibrotic in comparison to typical ICC (8, 19, 21), the amount of fibrotic tissue in HCC would not reach that in HICC, which reflects the difference in the CT value in the EP.

The difference between HICC and HCC in the UP is likely due to the different cell densities of tumors. Higher cellularity of tissues is reported to be associated with hyperdensity in the UP (22, 23). As cellularity in HICC decreases in proportion to the degree of intratumoral desmoplasia, HICC does not have as many tumor parenchymal cells as HCC. In addition, the histopathological type of ICC seems to have the potential to decrease the cellularity of the tumor. As most of the HICCs in the present study (86%) were well-to-moderately differentiated tubular adenocarcinoma, elongated or tortuous glands and their fluid content make ICCs a sparse tumor at the cellular level. The histopathological features, including the type of tumor cell, cellular density, stromal tissue reaction, and the tubular adenocarcinoma content might lead to unique tumor microenvironments, causing discrepancy in the CT values in the UP between HICC and HCC. Other than the cellularity of the tumor, the amount of fatty change, fibrotic change, or necrotic change will affect the CT value in the UP. HCC sometimes shows sporadic fatty tissue and necrosis (1, 24), and ICC often develops tumor necrosis or fibrotic scarring (4, 25). In addition to the cellularity of the tumor, various factors influence the CT value of the tumor in the UP.

The correct preoperative differentiation between hypervascular-type ICC and HCC is of great significance for treatment strategies and the assessment of the prognosis. Only 13 of 22 patients (59%) in HICC group were diagnosed correctly before hepatectomy. It is well known that ICC has a tendency to spread along the major Glissonean branches or invade the wall of large vessels (15, 25-27). On the other hand, several authors have reported that marginal resection is acceptable for solitary HCC with or without a cirrhotic liver (28, 29). Thus, in the surgical treatment for ICC, resection with a wide surgical margin without any tumor exposure and a frozen section examination of the Glissonean stump should be added. In addition, lymph node metastasis is relatively common in ICC (15). It is true that several authors recently mentioned that the incidence of lymph node metastasis in patients with HICC was not so high in comparison to hypovascular ICC (7, 11, 30, 31), it is important to at least consider sampling the lymph nodes in

Table II. *The results of the univariate and multivariate analyses to identify independent factors for the differential diagnosis of HICC and HCC.*

			Univariate	Multivariate	
Variables	HICC (n-22)	HCC (n=120)	*p*-Value	Odds ratio (95%CI)	*p*-Value
Gender			0.106		
Male	13	99			
Female	9	27			
Age			0.643		
<70 years	10	64			
≥70 years	12	56			
HBV-Ag			1		
Present	3	21			
Absent	19	99			
HCV-Ab			0.032		
Present	4	53			
Absent	18	67			
CEA (ng/ml)			0.314		
<5	16	50			
≥5	5	8			
CA19-9 (U/ml)			0.03		
<37	12	42			
≥37	9	8			
AFP (ng/ml)			<0.001		
<10	16	49			
≥10	3	71			
PIVKA (mAU/ml)			<0.001		
<40	18	29			
≥40	0	90			
Non-tumorous liver			<0.001	6.35 (1.97-20.5)	0.002
NL	11	15			
CH/LF/LC	11	105			
Tumor size (mm)			0.244		
<40	7	57			
≥40	15	63			
CT value of the tumor in UP (HU)			0.027		
<43	16	46			
≥43	6	74			
CT value of the tumor in LAP (HU)					
<95	8	55	0.488		
≥95	14	65			
CT value of the tumor in PVP (HU)			0.196		
<110	13	89			
≥110	9	31			
CT value of the tumor in EP (HU)			0.002		
<100	12	103			
≥100	10	17			
E/U ratio (>2.3 *vs.* <2.3)			<0.001	13.1 (4.28-39.8)	<0.001
<2.3	7	104			
≥2.3	15	16			

HICC: Hypervascular intrahepatic cholangiocarcinoma; HCC: hepatocellular carcinoma; CI: confidence interval; BMI: body mass index; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; CEA: carcinoembryonic antigen; CA19-9: cancer-associated carbohydrate antigen 19-9; AFP: alfa-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; NL: normal liver; CH: chronic hepatitis; LF: liver fibrosis; LC: liver cirrhosis; CT: computed tomography; HU: Hounsfield unit; UP: unenhanced phase; LAP: late arterial phase; PVP: portal vein phase; EP: equilibrium phase.

hepatoduodenal ligament because lymph node metastasis is an important prognostic factor in ICC (15, 32, 33-35).

The present study is associated with several limitations. First, the CT value in the enhancement phases can be influenced by various factors including the type of CT scanner, contrast protocol, reconstruction algorithm, and measurement site (36, 37). Second, this measurement is not available for patients who have undergone pre-surgical treatment or small

tumors that are unmeasurable in multi-slices. Furthermore examination under the same protocol will be needed to confirm that our result is sufficient in different settings.

In conclusion, we examined the CT value of ICC showing a hypervascular appearance in the LAP on multi-phase enhanced CT, and clarified that HICC had a lower CT value in the UP and higher CT value in the EP in comparison to HCC in the corresponding phases. Even if the tumor develops enhancement in the LAP, an E/U ratio of >2.3 should be considered a risk factor for HICC in non-cirrhotic patients, and appropriate surgical treatment including extended hepatectomy or lymph node dissection would be necessary.

Conflicts of Interest

None declared.

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